Development of CNS multi-receptor ligands: Modification of known D_2 pharmacophores

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ABSTRACT

Several known D_2 pharmacophores have been explored as templates for identifying ligands with multiple binding affinities at dopamine and serotonin receptors considered as clinically relevant receptors in the treatment of neuropsychiatric diseases. This approach has resulted in the identification of ligands that target multiple CNS receptors while avoiding others associated with deleterious effects. In particular, compounds **11**, **15** and **22** may have potential for further development as antipsychotic agents as they favorably interact with the clinically relevant receptors including D_2R, 5-$HT_{1A}R$, and 5-HT_7R. We have also identified the pair of compounds **11** and **10** as high affinity D_2R ligands with and without SERT binding affinities, respectively. These differential binding profiles endow the pair with the potential for evaluating SERT contributions to antipsychotic drug activity in animal behavioral models. In addition, compound **11** has no significant affinity for 5-$HT_{2C}R$ and binds only moderately to the H_1R, suggesting it may not induce weight gain or sedation when used clinically. Taken together, compound **11** displays an interesting pharmacological profile that necessitates the evaluation of its functional and in vivo effects in animal models which are currently ongoing.

1. Introduction

The dopamine D_2 receptor (D_2R) has long been considered the target for drug development in schizophrenia and other neuropsychiatric diseases.[1] More recently, however, several neuropsychiatric illnesses are being viewed as multiple receptor pathological diseases, meaning that effective drugs designed to treat these diseases must target several receptors simultaneously.[2–6] This view is supported, for example, by the fact that a neuropsychiatric disease like schizophrenia manifests at least three different symptoms: positive, negative and cognitive symptoms. While blocking D_2R has been associated with treating the positive symptoms, the negative and cognitive symptoms remain unresolved.[7,8] Several recent articles have indicated that the negative symptoms of schizophrenia may be ameliorated by activating the serotonin 5-HT_{1A} receptor (5-$HT_{1A}R$)[9–13] while the cognitive symptoms may be treated by agents that activate the 5-$HT_{1A}R$ and antagonize the 5-HT_7 receptor (5-HT_7R).[14–18] Taken together, we hypothesize that a drug that interacts appropriately with these receptors should have improved therapeutic outcomes over several currently marketed drugs for treating schizophrenia. Indeed, one of the most recent drugs introduced on the market, lurasidone, targets multiple receptors including D_2, 5-HT_{2A}, 5-HT_7 and 5-HT_{1A}, and has found clinical utility not only in treating the positive symptoms of schizophrenia but also in producing improvement in cognitive symptoms, and is even prescribed for bipolar depression.[19,20]

Our laboratory has been involved in multi-receptor targeting as possible treatment options for CNS diseases over the years.[2,21,22] In this article, we explored different modifications to pharmacophoric groups (Fig. 1) present in ligands that have high affinity for CNS receptors or elaborated structurally similar functionalities to such pharmacophores. The working hypothesis was that by modifying the arylalkyl groups attached to the amino groups in the pharmacophores shown in Figure 1, it was possible to broaden the affinity of a target compound to other CNS receptors including the D_2R, 5-$HT_{1A}R$, 5-HT_7R and SERT. In view of the role of the D_2R as a

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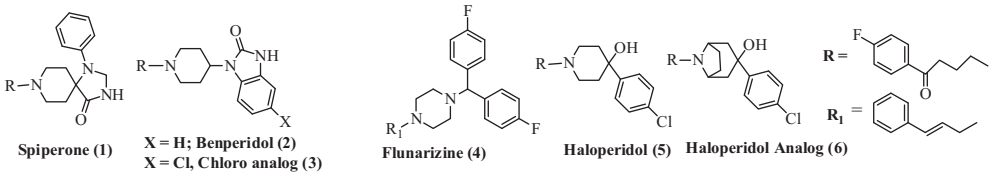


Figure 1. Structures of standard drugs and the pharmacophoric groups (R = R_1 = H) used in obtaining the target compounds.

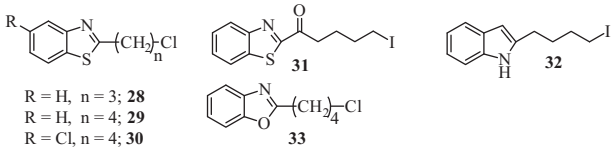


Figure 2. Alkylating agents **28**–**33**.

primary target for drug development against neuropsychiatric diseases including schizophrenia and bipolar depression, it was of interest to first obtain agents that had moderate to high affinity to the D_2R ($10 \geqslant K_i \leqslant 250$ nM) before introducing structural features that lead to binding at the other receptors of interest. We also intended to identify compounds that while binding to these receptors will simultaneously have low or little affinities at 5-HT_{2B}R, 5-HT_{2C}R and histamine H-1 receptors as these have been associated with known side effects including valvular heart disease,[23–25] weight gain[26–28] and sedation.[26–28]

2. Chemistry

The pharmacophoric groups (R = R_1 = H) in **1**, **3**, **4** and **5** were commercially available from Sigma/Aldrich. Pharmacophore **6** was previously synthesized.[29–31] To synthesize the target compounds **7**–**22**, different alkylating agents were required as depicted in Figure 2. Alkylating groups **28**–**29** were obtained by reacting 5-chloropentanoyl chloride or 4-chlorobutanoyl chloride with 2-aminobenzenethiol as previously reported,[21,32] while **30** was synthesized from 2-amino-4-chlorobenzenethiol and 5-chloropentanoyl chloride using the same procedure.

We also previously reported the synthesis of alkylating agent **31**[21,32] while **32** was obtained by following a literature procedure.[33–37] Briefly, 4-(1*H*-indol-3-yl)butanoic acid was reduced by lithium aluminum chloride and the resulting primary alcohol converted to the iodide (**32**) using triphenylphosphine (Ph_3P) and iodine in CH_2Cl_2. The benzoxazole alkylating agent **33** was synthesized following the literature procedure we reported earlier.[38] 6-Chlorohexanoyl chloride or 5-chloropentanoyl chloride were each reacted with 2-aminophenol in the presence of triethylamine (Et_3N) and heated to reflux to provide the amide intermediate which underwent cyclization with polyphosphoric acid (PPA) to produce the resulting alkylating agent **33** in good yield.

3. Results and discussion

The pharmacophoric groups in spiperone (**1**), the chloro analog of benperidol (**3**), haloperidol (**5**) and the tropane analog of haloperidol (**6**) in Figure 1 constituted the group of starting fragments selected because of their association with high affinity binding to the D_2 receptor.[29–31] The flunarizine pharmacophore (**4**) was also included for evaluation as flunarizine has been shown to demonstrate multiple CNS actions.[39] We have hypothesized that by attaching various aryl alkyl groups to these pharmacophores, it is possible to obtain compounds which can bind to the D_2R and other clinically relevant receptors including 5-HT_{1A}R and 5-HT_7R. In particular, it was of interest to attach aryl (benzothiazole-, benzoxazole- and indole-) alkyl groups in view of their observed effects on binding affinity to CNS receptors.[21,32,38]

The first group of compounds (Fig. 3), **7**–**11**, were obtained by the alkylation of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (**2**) with the appropriate arylalkyl group (Schemes 1–4), and their binding affinity constants are reported in Table 1. Compound **7** showed potent binding to the D_2R but only moderate to weak binding affinities to the 5-HT receptors evaluated. Introduction of a chloro group onto the benzothiazole ring (**8**) to explore the effect of an electron withdrawing group on the ring electron density did not produce any significant changes in binding affinity. Similarly, insertion of a carbonyl moiety (**9**) had no significant effect. Furthermore, replacement of the benzothiazole with either benzoxazole (**10**) or indole (**11**) moieties failed to extend significant increase in affinity to the 5-HT receptors. Based on their overall binding profile at these receptors, group 1 compounds could, in general, be classified as showing selectivity to the D_2 and D_3 receptors (K_i range 10–32 nM) while binding to the D_4R is mixed, with **11** showing the highest binding affinity (K_i = 1.6 nM) and compound **8** the lowest (K_i = 1512 nM). Compounds **8** and **9** bind with moderate affinity to the 5-HT_{1A}R (K_i = 102 and 103 nM, respectively) and combined with their high affinity to the D_2R, could serve as useful agents for further exploration.

5-Chloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one, the pharmacophore of **3**, was next selected for alkylation and resulted in compounds **12**–**15**. These along with compounds **16** and **17** constitute group 2 analogs (Fig. 4, Schemes 1–4). Synthesis and subsequent screening produced the binding affinity data reported in Table 2. Compound **12** has about 9-fold lower affinity to the D_2R (K_i = 215 nM) compared to the corresponding analog in group 1 (compound **7**) suggesting that the triazaspiro[4.5]decan-4-one (pharmacophore **2**) has a better affinity for the D_2R than

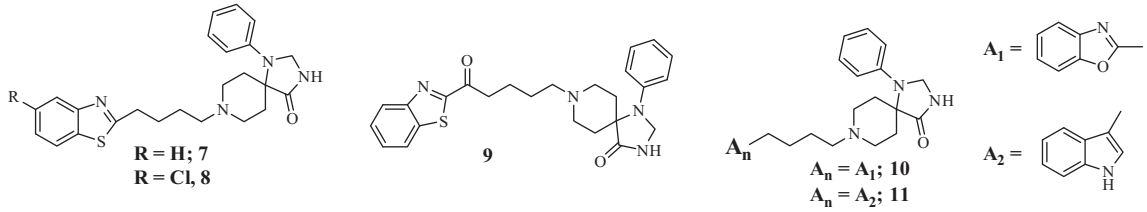
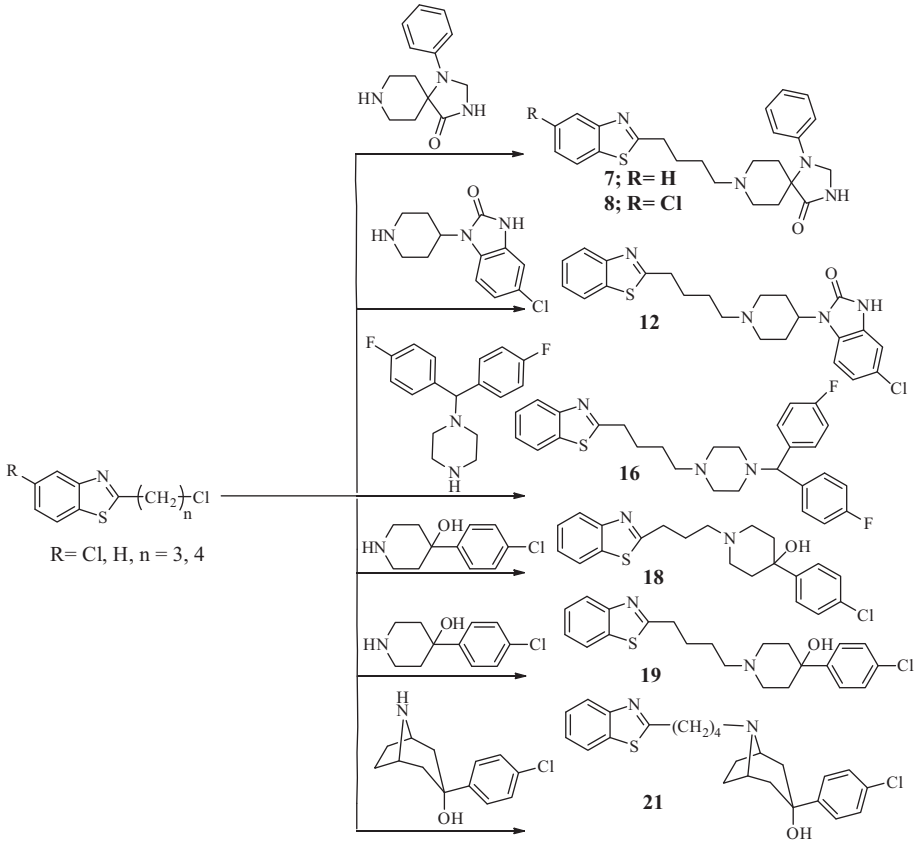


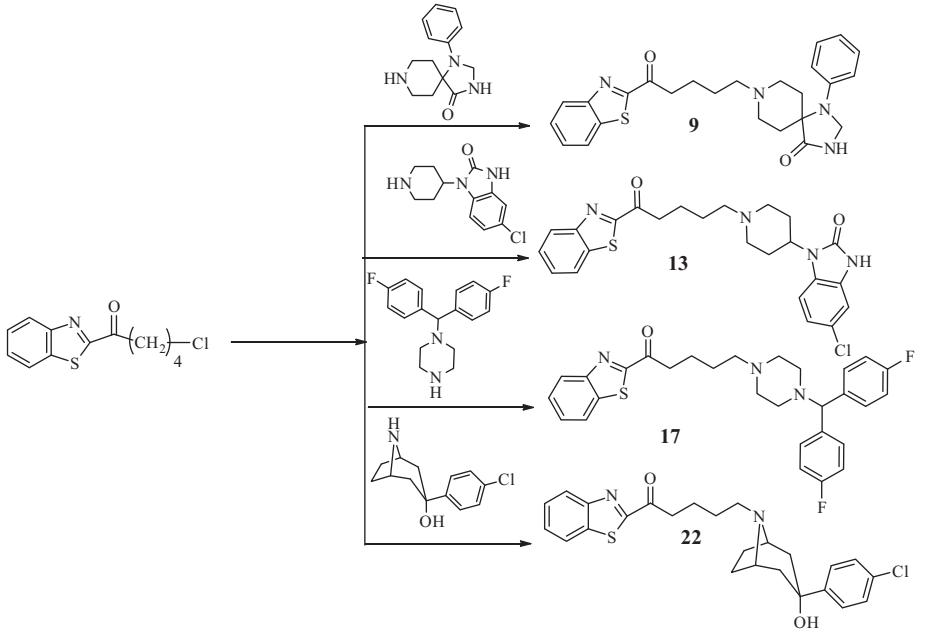
Figure 3. Structures of target compounds in group 1.



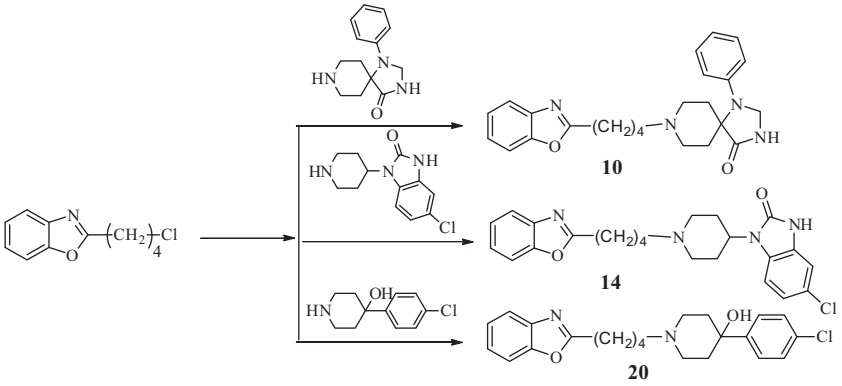
Scheme 1. Synthesis of target compounds **7**, **8**, **12**, **16**, **18**, **19**, and **21**. Reagents and conditions: (i) K_2CO_3, KI, CH_3CN/DME, reflux, 12–15 h.

pharmacophore **3.** Indeed, compounds **13–15** which utilize pharmacophore **3** display lower binding affinity compared to the corresponding analogs in group 1. In addition, the binding of the group 2 compounds had only moderate to poor binding to the selected 5-HT receptors.

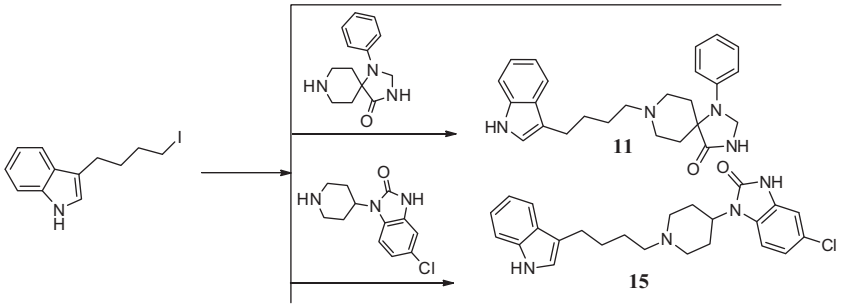
We also evaluated two piperazine analogs utilizing the 1-(bis (4-fluorophenyl)methyl)-piperazine, pharmacophore from **4**. Alkylating this group with the previous benzothiazole-alkyl groups produced compounds **16** and **17** which bind to the D_2R with moderate affinities (K_i = 195.0 and 159.0 nM, respectively). Like



Scheme 2. Synthesis of target compounds **9**, **13**, **17** and **22**. Reagents and conditions: (i) K_2CO_3, KI, CH_3CN/DME, reflux, 12–15 h.



Scheme 3. Synthesis of target compounds **10**, **14** and **20**. Reagents and conditions: (i) K_2CO_3, CH_3CN, reflux, 12–15 h.



Scheme 4. Synthesis of target compounds **11** and **15**. Reagents and conditions: (i) K_2CO_3, CH_3CN, reflux, 12–15 h.

Table 1
Binding affinity (K_i nM/pK_i ± SE) of group 1 compounds at selected DA and 5-HT receptors[a]

Compound	K_i (nM)/pK_i ± SE					
	D_2	D_3	D_4	5-HT_{1A}	5-HT_{2A}	5-HT_7
7	24.0/7.62 ± 0.04	32.0/7.49 ± 0.06	132.0/6.88 ± 0.04	195/6.71 ± 0.07	>10,000/N/A	626.0/6.2 ± 0.1
8	18.0/7.74 ± 0.08	499.0/6.3 ± 0.07	1512.0/5.8 ± 0.1	102.0/6.99 ± 0.06	1123.0/5.8 ± 0.1	1598.0/5.8 ± 0.1
9	25.0/7.59 ± 0.07	18.0/7.75 ± 0.04	162.0/6.79 ± 0.05	103.0/6.99 ± 0.04	3720.0/5.43 ± 0.04	518.0/6.29 ± 0.05
10	10.0/7.99 ± 0.04	21.0/7.68 ± 0.05	118.0/6.93 ± 0.04	382/6.42 ± 0.07	MTA	1511/5.8 ± 0.1
11	22.0/7.65 ± 0.06	31.0/7.5 ± 0.1	1.6/8.81 ± 0.05	376.0/6.42 ± 0.07	982.0/6.01 ± 0.07	>10,000
Spiperone	0.16 ± 0.02[b]	0.32 ± 0.04[c]	1.4 ± 0.5[c]	17.2 ± 3.8[d]	1.1 ± 0.07[e]	110 ± 17[f]

N/A = Not available. Data points without SE have errors below 20% of the mean.
[a] MTA = Missed 50% threshold inhibition.
[b] Ref. 40.
[c] Ref. 41.
[d] Ref. 42.
[e] Ref. 43.
[f] Ref. 44.

the other group 2 analogs, D_2R binding affinity was lower along with weak affinity to the 5-HT receptors evaluated. Overall, the group 2 analogs have D_2R binding affinity constants below 250 nM, varying moderate to high binding affinities at the D_3 (K_i = 33–233 nM) and D_4 (K_i = 16–1710 nM) receptors and relatively poor binding to the 5-HT receptors.

Compounds in group 3 (Fig. 5) are obtained by alkylating 4-chlorophenyl piperidinol or tropanol pharmacophores from **5** and **6**. We have previously shown that these pharmacophores can be manipulated to control their CNS receptor binding profiles.[29–31] Using the previously synthesized benzothiazole- or benzoxazole-linked alkyl groups, 4-chlorophenyl piperidinol was targeted for alkylation to produce compounds **18**–**20** (Schemes 1–3). These compounds were synthesized and screened at the same receptors as before and the results are reported in Table 3. Apart from compound **19** with moderate binding affinity (K_i = 201 nM) none of the other four analogs meets the D_2 binding criterion. Other than compound **18** which binds with relatively high affinities at the 5-$HT_{1A}R$ and 5-HT_7R (K_i = 34.0 and 189.0 nM, respectively), there were no significant improvements in binding at the 5-HT receptors. Finally, the tropane analogs **21** and **22** were synthesized and similarly screened. Compound **21** binds with high affinity at the D_2R and D_3R (K_i = 44.0 and 13 nM, respectively) but binds poorly to the D_4R and 5-HT receptors. Compound **22** on the other hand binds with moderate affinity to the D_2R (K_i = 180.0 nM) and with even higher affinity at the 5-HT_7R (K_i = 80.0 nM). Overall, the group 3 analogs have high to moderate binding to the D_2R and variable binding affinities to the 5-HT receptors evaluated.

In view of the fact that D_2R ligands with favorable interactions at 5-$HT_{1A}R$, 5-$HT_{2A}R$, 5-HT_7R and the serotonin transporter (SERT) have potential utility as effective agents for schizophrenia and

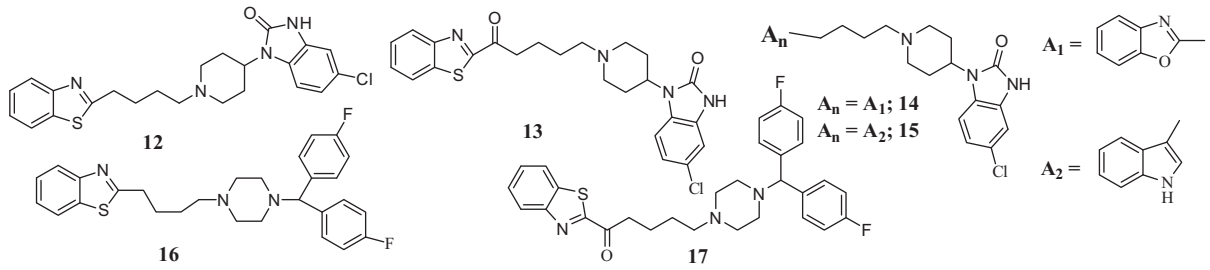


Figure 4. Structures of target compounds in group 2.

Table 2
Binding affinity (K_i nM/pK_i ± SE) of group 2 compounds at DA and 5-HT receptors[a]

Compound	K_i (nM)/pK_i ± SE					
	D_2	D_3	D_4	5-HT_{1A}	5-HT_{2A}	5-HT_7
12	215.0/6.67 ± 0.05	163.0/6.79 ± 0.06	671.0/6.17 ± 0.06	1162.5/N/A	>10,000/N/A	286.0/6.54 ± 0.06
13	217.0/6.66 ± 0.04	64.0/7.2 ± 0.04	1710.0/5.77 ± 0.07	252.0/6.6 ± 0.04	1564.0/5.81 ± 0.04	127.0/6.9 ± 0.05
14	95.0/7.02 ± 0.06	109.0/6.96 ± 0.06	841.0/6.08 ± 0.05	611/6.21 ± 0.05	3392.0/5.47 ± 0.05	313.0/6.5 ± 0.06
15	134.0/6.87 ± 0.07	53.0/7.3 ± 0.1	16.0/7.79 ± 0.06	MTA	MTA	111.0/6.95 ± 0.08
16	195.0/6.71 ± 0.07	33.0/7.5 ± 0.1	68.0/7.17 ± 0.05	MTA	519.0/6.28 ± 0.05	778.0/6.1 ± 0.1
17	159.0/6.8 ± 0.07	233.0/6.6 ± 0.1	1217.0/5.91 ± 0.05	MTA	1082.0/5.97 ± 0.07	562.0/6.3 ± 0.1
Benperidol*	0.027[b]	0.29 ± 0.02[c]	0.066[b]	N/A	1.2[d]	N/A

N/A = Not applicable or not available.
[a] MTA = Missed 50% inhibition threshold.
[b] Ref. 45.
[c] Ref. 46.
[d] Ref. 47.
* Only K_i values provided.

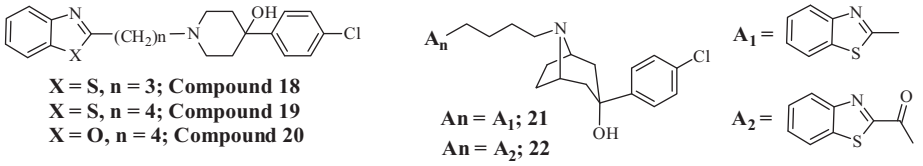


Figure 5. Structures of target compounds in group 3.

Table 3
Binding affinity (K_i nM/pK_i ± SE) of group 3 compounds at DA and 5-HT receptors[a]

Compound	K_i (nM)/pK_i ± SE					
	D_2	D_3	D_4	5-HT_{1A}	5-HT_{2A}	5-HT_7
18	763.0/6.12 ± 0.05	28.0/7.55 ± 0.09	163.0/6.79 ± 0.04	34.0/7.47 ± 0.04	168.0/6.78 ± 0.04	189.0/6.72 ± 0.08
19	201.0/6.7 ± 0.08	291.0/6.54 ± 0.06	140.0/6.85 ± 0.06	771.0/6.11 ± 0.08	4255.0/5.37 ± 0.06	983.0/N/A
20[b]	438 ± 28	942 ± 200	229 ± 49	3153 ± 368	5970 ± 1189	MTA
21	44.0/7.35 ± 0.03	13.0/7.89 ± 0.6	432.0/6.36 ± 0.09	274.0/6.60 ± 0.06	>10,000	1009/6.0 ± 0.07
22	180.0/6.74 ± 0.07	16.0/7.79 ± 0.07	508.0/6.29 ± 0.09	MTA	MTA	80.0/7.1 ± 0.08
Haldol **5***	0.89/9.05 ± 0.30	2.5/8.61 ± 0.05	10.0/7.98 ± 0.28	3600/5.44 ± 0.03	120.0/6.91 ± 0.02	1100/5.95 ± 0.13
Analog **6***,[b]	1.6 ± 0.14	5.1 ± 3.0	5.3 ± 0.99	27.7 ± 8.0	30.9 ± 6.0	ND

ND = Not determined. N/A = Not applicable. Data points without SE have errors below 20% of the mean.
[a] MTA = Missed 50% threshold inhibition.
* Previously reported in Refs. 2,48.
[b] Only K_i values provided.

bipolar depression for example, compounds **7**–**11**, **14**, **15**, **21** and **22** were selected for further evaluation at other receptors associated with improved pharmacological profile and the results are recorded in Table 4. The binding affinities of these compounds at other receptors associated with the undesirable side effects (5-HT_{2B}, 5-HT_{2C} and H_1 receptors) are also reported.

We have hypothesized that compounds which simultaneously interact with the D_2R and, for example, either the 5-HT_7R or SERT, have the potential to augment the effectiveness of primarily single receptor agents used in the treatment of schizophrenia or bipolar depression. Evaluation of the data in Table 4 shows that compounds **8** (D_2R and 5-HT_{1A}R), **9** (D_2R and 5-HT_{1A}R), **11** (D_2R and SERT), **15** (D_2R and SERT), and **22** (D_2R, 5-HT_7R and SERT) may have potential utility as hits in the development of agents for the treatment of schizophrenia and bipolar depression, depending on their functional status. In addition, while both compounds

Table 4
Binding affinity (K_i nM/pK_i ± SE) of selected compounds at CNS receptors[a] and their *c*log*P* values[b]

Receptor	K_i (nM)/pK_i ± SE								
	7	**8**	**9**	**10**	**11**	**14**	**15**	**21**	**22**
D_2R	24/7.62 ± 0.04	18/7.74 ± 0.08	25/7.59 ± 0.07	10/7.99 ± 0.04	22/8.86 ± 0.06	95/7.02 ± 0.06	134/8.57 ± 0.07	44/7.35 ± 0.03	180/6.74 ± 0.07
$5HT_{1A}R$	195/6.71 ± 0.07	102/6.99 ± 0.06	103/6.99 ± 0.04	382/6.42 ± 0.07	376/6.4 ± 0.1	611/6.21 ± 0.05	MTA	274/6.60 ± 0.06	MTA
$5HT_{2A}R$	>10K	1123/5.8 ± 0.1	3720/5.43 ± 0.04	MTA	982/7.65 ± 0.06	3392/5.47 ± 0.05	MTA	>10K	MTA
$5HT_{2B}R$	122/6.91 ± 0.06	36/7.44 ± 0.08	1578/5.8 ± 0.1	905/6.04 ± 0.08	202/6.69 ± 0.08	515/6.29 ± 0.06	51/7.29 ± 0.07	342/6.47 ± 0.06	758/6.12 ± 0.09
$5HT_{2C}R$	MTA	614/6.21 ± 0.08	MTA	MTA	MTA	MTA	MTA	4623/5.34 ± 0.09	MTA
$5HT_7R$	626/6.2 ± 0.1	1598/5.8 ± 0.1	518/6.29 ± 0.05	1511/5.82 ± 0.09	>10K	313/6.5 ± 0.06	111/6.95 ± 0.08	1009/6.0 ± 0.07	80.0/7.1 ± 0.08
SERT	MTA	3056/5.51 ± 0.06	284/6.55 ± 0.07	MTA	10.0/8.33 ± 0.05	386/6.41 ± 0.06	25/7.6 ± 0.04	180/6.74 ± 0.08	54.0/8.33 ± 0.05
H_1R	504/8.93 ± 0.07	263/6.56 ± 0.06	ND	535/6.27 ± 0.09	273/6.56 ± 0.07	510/6.3 ± 0.1	255/6.61 ± 0.06	187/6.73 ± 0.08	1028/5.99 ± 0.08
*c*Log*P*	2.48	4.37	3.35	2.57	3.51	4.47	5.42	5.48	5.20

ND = Not determined.
[a] MTA = missed 50% threshold inhibition.
[b] *c*Log*P* values were estimated using ChemDraw 12.0.

11 and **10** bind with high affinities to D_2R, **11** binds with high affinity to SERT but **10** is without significant affinity to SERT. This differential binding profile endows the pair with the potential for evaluating SERT contributions in animal behavioral studies. Furthermore, compound **11** has the desirable profile of no significant affinity for 5-$HT_{2C}R$ and only moderate binding to the H_1R.

Since the compounds are designed to target CNS receptors, we also estimated some of the key physicochemical characteristics including their *c*log*P* values using ChemDraw version 12 as reported in Table 4. Apart from compounds **15**, **21** and **22** all the other compounds have estimated *c*log*P* values below 5.0. Compound **11**, which displays the most interesting binding affinity profile, was further compared with haloperidol and spiperone and the results indicate compound **11** (log*P* = 3.52; *c*log*P* = 3.51; tPSA = 47.61) compares favorably with haloperidol (log*P* = 3.49; *c*log*P* = 3.85; tPSA = 40.54) and spiperone (log*P* = 2.78; *c*log*P* = 2.82; tPSA = 52.65) in terms of their lipophilicity (*c*log*P*/log*P*) and topological polar surface area (tPSA) values. Overall, both the pharmacological and physicochemical profiles of these compounds suggest further evaluation of their functional activities at the respective receptors and in vivo animal testing to further ascertain their true potentials as leads for preclinical examination.

4. Conclusion

By modifying the arylalkyl groups attached to various CNS pharmacophores, we have demonstrated that receptor binding profiles of these agents can be obtained that could form the basis of identifying multi-receptor targeting ligands. Several of the compounds have desirable multi-receptor binding profiles to receptors of interest. In particular, compounds **11**, **15** and **22** may have potential utility as leads for further optimization to treat schizophrenia and bipolar disorders depending on their functional status. We have also identified compounds **11** and **10** as high affinity D_2R ligands with and without SERT binding affinities, respectively, which suggests that they may have a great potential for evaluating SERT contributions in animal behavioral studies. Compound **11** has no significant affinity for 5-$HT_{2C}R$ and binds only moderately to the H_1R suggesting little or no induction of sedation or weight gain. In addition, compound **11**'s physicochemical characteristics as calculated by ChemDraw, are consistent with drugs that cross the BBB and elicit their pharmacological properties in the CNS.

5. Methods

5.1. Reagents and general procedures

Melting points were determined on a Gallenkamp (UK) apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian 300 MHz Mercury Spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, and are within 0.4% of theory unless otherwise noted. Flash chromatography was performed on Combi-Flash (Teledyne Isco) using RediSep normal phase silica columns. N,N-dimethylformamide was distilled from $CaSO_4$ and stored over 4 Å molecular sieves. Starting materials were obtained from either Sigma–Aldrich or VWR and were used without further purification.

5.2. General procedure for the synthesis of alkylating agents (28–30)

To a solution of 2-aminothiophenol (5 g, 39.9 mmol) or 2-amino-4-chlorobenzenethiol in toluene (100 mL), 5-chlorobutanoyl chloride or 5-chloropentanoyl chloride (43.9 mmol) was added drop wise over a 15 min period during which an off-white precipitate was formed. After the reaction mixture was stirred at room temperature (rt) overnight, water (100 mL) was added, the two layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extract was washed with water (100 mL) and saturated NaCl solution (100 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified on Combiflash using EtOAc/Hexanes, to yield 2-(3-chloropropyl)benzo-[*d*]thiazole **28** or 2-(4-chlorobutyl)benzo [*d*]thiazole **29** as an oily liquid or 5-chloro-2-(4-chlorobutyl) benzo[*d*]thiazole (**30**) as a solid.

5.2.1. 2-(3-Chloropropyl)benzo[*d*]thiazole (28)

Oily liquid, yield: 72%, ^{1}H NMR (CD_3OD): δ 8.14 (d, 1H, *J* = 4.1 Hz), 8.02 (d, 1H, *J* = 4.1 Hz), 7.72–7.59 (m, 2H), 3.64–3.57 (m, 2H), 3.38–3.28 (m, 2H), 1.95–1.86 (m, 2H).

5.2.2. 2-(4-Chlorobutyl)benzo[*d*]thiazole (29)

Oily liquid, yield 56%, ^{1}H NMR ($CDCl_3$): δ 7.98–7.95 (m, 1H), 7.85e7.82 (m, 1H), 7.48–7.42 (m, 1H), 7.37–7.32 (m, 1H), 3.60 (t, 2H, *J* = 7.5 Hz), 3.15 (t, 2H, *J* = 7.5 Hz), 2.09–1.97 (m, 2H), 1.95–1.90 (m, 2H).

5.2.3. 5-Chloro-2-(4-chlorobutyl)benzo[*d*]thiazole (30)

Solid, yield: 89%, mp: 110 °C, ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1H, *J* = 2.1 Hz), 7.74 (d, 1H, *J* = 8.1 Hz), 7.35–7.32 (dd, 1H, *J* = 1.8, 6.6 Hz), 3.56 (t, 2H, *J* = 6.0 Hz), 3.15 (t, 2H, *J* = 7.5 Hz), 2.08–2.00 (m, 2H), 1.96–1.89 (m, 2H).

5.3. Procedure for the synthesis of 3-(4-iodobutyl)-1*H*-indole (32)

The synthesis of 3-(4-iodobutyl)-1*H*-indole followed literature procedures.[36,49] To a solution of indole-3-butyric acid (2 g, 9.8 mmol) dissolved in THF (30 mL) and cooled to 0 °C was added

portionwise $LiAlH_4$ (2.24 g, 59.0 mmol, 6 equiv) in THF. The mixture was allowed to warm to room temperature with stirring for 18 h. The reaction mixture was cooled to 0 °C and a saturated solution of Na_2SO_4 (20 mL) was added in a dropwise manner over the period of 30 min. The resulting white precipitate was filtered, the filtrate was washed with EtOAc (2 × 100 mL), the pooled organic phase was washed with water (50 mL) and saturated brine solution (50 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The crude product 3-(4-hydroxybutyl)-1*H*-indole was obtained as a colorless solid and used for the next step without further purification (1.70 g), Yield: 91%, mp: 32–33 °C. ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.60 (d, 1H, *J* = 7.8 Hz), 7.36–7.33 (m, 1H), 7.21–7.08 (m, 2H), 6.97 (s, 1H), 3.67 (t, 2H, *J* = 6.3 Hz), 2.79 (t, 2H, *J* = 7.5 Hz), 1.84–1.63 (m, 4H). To a stirred solution of triphenylphosphine (4.46 g, 17.0 mmol) and imidazole (1.58 g, 17.0 mmol) in dichloromethane (DCM) (45 mL) cooled to 0 °C, was added I_2 (4.32 g, 17.0 mmol) and the reaction mixture was stirred at 0 °C for 30 min. Thereafter, a solution of 3-(4-hydroxybutyl)-1*H*-indole (2.30 g, 12.15 mmol) in DCM (5 mL) was added, the reaction mixture was allowed to warm to rt with stirring for 12 h, then filtered and the filtrate was washed with hexane (2 × 100 mL). The combined organic solution was washed with water (100 mL) and saturated brine (80 mL) before being dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified on CombiFlash using EtOAc/hexanes as eluent. The pure product 3-(4-iodobutyl)-1*H*-indole was isolated as an oily liquid (2.40 g), Yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (s, 1H). 7.59 (d, 1H, *J* = 8.1 Hz), 7.35 (d, 1H, *J* = 8.1 Hz), 7.22–7.17 (t, 1H, *J* = 6.9 Hz), 7.12 (m, 1H), 6.97 (d, 1H, *J* = 2.1 Hz), 3.22 (t, 2H, *J* = 6.9 Hz), 2.84 (t, 2H, *J* = 6.9 Hz), 1.96–1.76 (m, 4H).

5.4. General alkylation procedure for compounds (7–12)

The procedure previously reported by us was followed.[16] A mixture of 2-(3-chloropropyl)benzo[*d*]thiazole (**28**) (1.3 mmol), or the appropriate alkylating agent (**29** or **30**), the appropriate amine (1.33 mmol), KI (100 mg), K_2CO_3 (13.3 mmol), and CH_3CN (15 mL) was heated to reflux for 12–24 h. The reaction progress was monitored by TLC and at completion, the mixture was cooled to rt, solvent removed, the resulting residue loaded onto a cartridge and purified by flash chromatography using EtOAc/hexane (9:1) to give the pure desired products. The hydrochloride salts where necessary were prepared by dissolving each pure compound in an appropriate solvent, adding excess ethereal HCl solution, removing solvent under reduced pressure, and recrystallizing the residue from an appropriate solvent.

5.4.1. 8-(4-(Benzo[*d*]thiazol-2-yl)butyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (7)

Yield: 32.4%, mp: 184–185 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.03–8.00 (m, 1H), 7.93–7.89 (m, 1H), 7.48–7.43 (m, 1H), 7.39–7.34 (m, 1H), 7.22–7.16 (t, 2H, *J* = 10.2 Hz), 6.81 (d, 2H, *J* = 7.8 Hz), 6.73–6.68 (t, 1H, *J* = 7.2 Hz), 4.54 (s, 2H), 3.16–3.11 (t, 2H, *J* = 7.8 Hz), 2.71–2.46 (m, 6 Hz), 2.39–2.34 (t, 2H, *J* = 7.2 Hz), 1.90–1.80 (m, 2H), 1.60–1.51 (m, 4H). *Calcd for*: $C_{24}H_{28}N_4OS{\cdot}0.2H_2O$: C, 67.96; H, 6.65; N, 13.21; Found: C, 67.95; H, 6.70; N, 12.94.

5.4.2. 8-(4-(5-Chlorobenzo[*d*]thiazol-2-yl)butyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (8)

Yield: 40%, mp: 206–208 °C, ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.08–8.05 (d, 1H, *J* = 9.0 Hz), 8.00 (d, 1H, *J* = 1.8 Hz), 7.46–7.42 (dd, 1H, *J* = 1.8, 8.4 Hz), 7.22–7.17 (dd, 2H, *J* = 1.2, 7.2 Hz), 6.83–6.81 (d, 1H, *J* = 8.1 Hz), 6.74–6.69 (t, 1H, *J* = 7.5 Hz), 4.55 (s, 2H), 3.29 (s, 2H), 3.18–3.13 (t, 2H, *J* = 7.5 Hz), 2.71–2.62 (m, 4H), 2.39–2.34 (t, 2H, *J* = 7.5 Hz), 1.87–1.82 (m, 2H), 1.55–1.51 (m, 4H). *Calcd for* $C_{24}H_{27}ClN_4OS{\cdot}0.1H_2O$: C, 63.10; H, 6.00; N, 12.26; Found: C, 62.85; H, 6.06; N, 12.17.

5.4.3. 8-(4-(Benzo[*d*]oxazol-2-yl)butyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (10)

Yield 56.2%, mp: 176–177 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (s, 1H), 7.67–7.61 (m, 2H), 7.33–7.30 (m, 2H), 7.19 (t, 2H, *J* = 7.5 Hz), 6.81 (d, 1H, *J* = 7.8 Hz), 6.70 (t, 1H, *J* = 7.2 Hz), 4.54 (s, 2H), 2.96–2.94 (t, 2H, *J* = 7.8 Hz), 2.70–2.50 (m, 6H), 2.35 (t, 2H, *J* = 7.5 Hz), 1.87–1.78 (m, 2H), 1.60–1.50 (m, 4H). *Calcd for*: $C_{24}H_{28}N_4O_2{\cdot}0.24H_2O$: C, 70.52; H, 6.90, N, 13.71; Found: C, 70.52; H, 6.85; N, 13.68.

5.4.4. 8-(4-(1*H*-Indol-3-yl)butyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (11)

Yield: 48.9%, mp: 208–210 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.79 (s, 1H), 9.03 (s, 1H), 7.52–6.80 (m, 10H), 4.61 (s, 2H), 3.70–3.17 (m, 4H), 2.80–2.62 (m, 6H), 2.00–1.50 (m, 6H). *Calcd for*: $C_{25}H_{30}N_4O{\cdot}0.3H_2O$: C, 73.61; H, 7.56; N, 13.73; Found: C, 74.00; H, 7.62; N, 13.39.

5.4.5. 1-(1-(4-(Benzo[*d*]thiazol-2-yl)butyl)piperidin-4-yl)-5-chloro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (12)

Yield: 24.2%, mp: 186–188 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.00 (s, 1H), 8.04–8.01 (m, 1H), 7.9–7.90 (m, 1H), 7.49–7.46 (dd, 1H, *J* = 1.5, 5.7 Hz), 7.40–7.35 (m, 1H), 7.18 (d, 1H, *J* = 8.1 Hz), 6.99–6.95 (dd, 2H, *J* = 2.1, 9.6 Hz), 4.14–4.00 (m, 1H), 3.12 (t, 2H, *J* = 7.2 Hz), 2.95 (d, 2H, *J* = 10.5 Hz), 2.35 (t, 2H, *J* = 7.5 Hz), 2.29–2.20 (m, 2H), 2.02–1.94 (m, 2H), 1.86–1.81 (m, 2H), 1.62–1.52 (m, 4H). *Calcd for*: $C_{23}H_{25}ClN_4OS{\cdot}0.66\ H_2O$: C, 61.00; H, 5.56; N, 12.37; Found: C, 60.99; H, 5.57; N, 11.99.

5.4.6. 1-(1-(4-(Benzo[*d*]oxazol-2-yl)butyl)piperidin-4-yl)-5-chloro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (14)

Yield: 34%, mp: 189–191 °C, ^{1}HNMR (300 MHz, DMSO-d_6): δ 7.67–7.63 (m, 2H), 7.35–7.30 (m, 2H), 7.18 (d, 1H, *J* = 8.1 Hz), 7.00–6.95 (m, 2H), 4.14–4.4.02 (m, 1H), 2.96 (t, 4H, *J* = 7.2 Hz), 2.34 (t, 2H, *J* = 6.9 Hz), 2.27–2.22 (m, 2H), 1.98 (t, 2H, *J* = 10.5 Hz), 1.80 (m, 2H), 1.61–1.49 (m, 4H). *Calcd for*: $C_{23}H_{25}ClN_4O_2{\cdot}0.5H_2O$: C, 63.66; H, 5.81; N, 12.91; Found: C, 63.52; H, 6.09; N, 12.76

5.4.7. 1-(1-(4-(1*H*-Indol-3-yl)butyl)piperidin-4-yl)-5-chloro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (15)

Yield: 40%, mp: 95–97 °C, ^{1}HNMR (300 MHz, $CDCl_3$): δ 9.16 (s, 1H), 7.99 (s, 1H), 7.62 (d, 1H, *J* = 7.5 Hz), 7.36 (d, 1H, *J* = 8.7 Hz), 7.22–7.07 (m, 4H), 7.02 (d, 2H, *J* = 8.7 Hz), 4.40–4.30 (m, 1H), 3.12 (d, 2H, *J* = 11.7 Hz), 2.80 (t, 2H, *J* = 7.2 Hz), 2.48 (t, 4H, *J* = 6.9 Hz), 2.15 (t, 2H, *J* = 12.3 Hz), 1.83–1.68 (m, 6H). *Calcd for*: $C_{24}H_{27}ClN_4O{\cdot}0.18EtOAc$: C, 65.69; H, 6.20; N, 12.77; Found: C, 65.66; H, 6.45; N, 12.34.

5.4.8. 2-(4-(4-(Bis(4-fluorophenyl)methyl)piperazin-1-yl)butyl) benzo[*d*]thiazole dihydrochloride(16)

Yield: 54.4%, hydroscopic, ^{1}H NMR (300 MHz, CD_3OD): δ 8.01–7.98 (m, 1H), 7.94–7.91 (m, 1H), 7.70–7.60 (m, 4H), 7.58–7.53 (m, 1H), 7.49–7.44 (m, 1H), 7.13 (t, 4H, *J* = 8.7 Hz), 5.14–5.00 (m, 1H), 3.60–3.52 (m, 4H), 3.32–3.25 (m, 10H), 2.04–1.82 (m, 4H). *Calcd for*: $C_{28}H_{31}Cl_2F_2N_3S{\cdot}0.75H_2O$: C, 59.62; H, 5.81; N, 7.45; Found: C, 59.45; H, 5.41; N, 7.28.

5.4.9. 1-(Benzo[*d*]thiazol-2-yl)-5-(4-(bis(4-fluorophenyl) methyl)piperazin-1-yl)pentan-1-one dihydrochloride (17)

Yield: 63.7%, hygroscopic, ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.10 (s, 1H), 8.15 (d, 1H, *J* = 7.8 Hz), 7.98–7.92 (m, 5H), 7.60–7.50 (m, 2H), 7.20–7.10 (m, 4H), 5.16 (s, 1H), 4.34 (br s, 2H), 4.14–4.05 (m, 2H),

3.68–3.58 (m, 2H), 3.35 (br s, 2H), 3.21 (br s, 2H), 2.06–1.94 (br s, 6H). *Calcd for*: $C_{29}H_{31}Cl_2F_2N_3OS{\cdot}H_2O$: C, 57.52; H, 5.66; N, 6.94; Found: C, 57.63; H, 5.60; N, 6.66

5.4.10. 1-(3-(Benzo[*d*]thiazol-2-yl)propyl)-4-(4-chlorophenyl) piperidin-4-ol hydrochloride (18)

Yield: 27%, mp 199–200 °C, ^{1}H NMR (DMSO-d_6): δ 10.89 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.38–7.52 (m, 6H), 5.59 (s, 1H), 3.42–3.46 (m, 2H), 3.16–3.26 (m, 6H), 2.37–2.45 (m, 2H), 2.27–2.35 (m, 2H), 1.74–1.79 (m, 2H). *Calcd for:* $C_{21}H_{24}Cl_2N_2OS$: C, 59.57; H, 5.71; N, 6.62; *Found*: C, 59.54; H, 5.71; N, 6.62.

5.4.11. 1-(4-(Benzo[*d*]thiazol-2-yl)butyl)-4-(4-chlorophenyl) piperidin-4-ol (19)

Yield: 17.5%, mp: 143–145 °C, ^{1}H NMR ($CDCl_3$): δ 7.79–7.94 (m, 1H), 7.86–7.83 (m, 1H), 7.48–7.42 (m, 3H), 7.38–7.29 (m, 3H), 3.16 (t, 2H, J = 7.8 Hz), 2.98–2.84 (m, 2H), 2.60–2.52 (m, 4H), 2.30–2.18 (m, 2H), 2.00–1.90 (m, 2H), 1.80–1.72 (m, 5H). *Calcd for*: $C_{22}H_{25}ClN_2OS$: C, 65.90; H, 6.28; N, 6.91; Found: C, 65.56; H, 6.17; N, 6.91.

5.4.12. 1-(4-(Benzo[*d*]oxazol-2-yl)butyl)-4-(4-chlorophenyl) piperidin-4-ol (20)

Yield: 49.5%, mp: 134–135 °C, ^{1}H NMR ($CDCl_3$): δ 7.67–7.64 (m, 1H), 7.49–7.46 (m, 1H), 7.43 (d, 2H, J = 9.0 Hz), 7.32–7.28 (m, 4H), 2.97 (t, 2H, J = 7.8 Hz), 2.80 (dd, 2H, J = 2.4, 8.7 Hz), 2.47 (t, 2H, J = 7.8 Hz), 2.37 (dd, 2H, J = 2.1, 9.6 Hz), 2.14–2.04 (m, 2H), 1.97–1.92 (m, 2H), 1.73–1.64 (m, 5H). *Calcd for*: $C_{22}H_{25}ClN_2O_2$: C, 68.65; H, 6.55; N, 7.28; Found: C, 68.39; H, 6.36; N, 7.10.

5.5. General procedure for the synthesis of compounds 21 and 22

A mixture of alkylating agent (**29** or **31**) (2.5 mmol), 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (680 mg, 2.85 mmol), K_2CO_3 (700 mg, 5.07 mmol) in DME (10 mL) was heated to reflux under N_2 for 16 h. The mixture was diluted with EtOAc (400 mL), washed with brine (50 mL) and the organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to dryness and column chromatographed on silica gel to afford the desired product. The product was converted into the HCl salt, followed by crystallization from MeOH–Et_2O to afford the pure HCl salt.

5.5.1. Synthesis of 8-(4-(benzo[*d*]thiazol-2-yl)butyl)-3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (21)

Yield 37%, mp: 198–200 °C, ^{1}H NMR (DMSO-d_6): 10.92 (1H, br s), 8.04 (1H, d, J = 8.1 Hz), 7.92 (1H, d, J = 8.1 Hz), 7.77 (2H, d, J = 8.4 Hz), 7.47 (1H, m), 7.40 (1H, m), 7.34 (2H, d, J = 8.4 Hz), 3.98 (2H, m), 3.15 (2H, m), 3.00 (2H, m), 2.63 (2H, m), 2.46 (4H, m), 2.08 (2H, m), 1.93 (6H, m). *Calcd for* $C_{24}H_{28}Cl_2N_2OS{\cdot}0.4H_2O$: C, 61.24; H, 6.00; N, 5.95; Found: C, 61.29; H, 6.05; N, 5.85.

5.5.2. 1-(Benzo[*d*]thiazol-2-yl)-5-(3-(4-chlorophenyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-pentan-1-one hydrochloride (22)

Yield 43%, mp: 202–204 °C, ^{1}H NMR (DMSO-d_6): 10.46 (1H, br s), 8.24 (2H, m), 7.73 (2H, d, J = 8.7 Hz), 7.64 (2H, m), 7.36 (2H, d, J = 9.0 Hz), 5.47 (1H, s), 4.30 (2H, m), 3.35 (4H, m), 3.14 (2H, m), 3.00 (2H, m), 2.57 (2H, m), 2.09 (2H, m), 1.88 (4H, m), 1.75 (2H, m). *Calcd for* $C_{25}H_{28}Cl_2N_2O_2S{\cdot}0.8H_2O$: C, 59.36; H, 5.58; N, 5.54; Found: C, 59.46; H, 5.82; N, 5.57.

5.5. Receptor binding studies

Binding affinities reported in Tables 1–4 were conducted by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP).[5] Details of the methods and radioligands used for the binding assays are available on the NIMH PDSP website at http://pdsp.med.unc.edu/UNC-CH%20Protocol%20Book.pdf.

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